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Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders.

Presta LG, Chen H, O'Connor SJ, Chisholm V, Meng YG, Krummen L, Winkler M, Ferrara N.

Department of Immunology, Genentech, Inc., South San Francisco, California 94080, USA.

Vascular endothelial growth factor (VEGF) is a major mediator of angiogenesis associated with tumors and other pathological conditions, including proliferative diabetic retinopathy and age-related macular degeneration. The murine anti-human VEGF monoclonal antibody (muMAb VEGF) A.4.6.1 has been shown to potently suppress angiogenesis and growth in a variety of human tumor cell lines transplanted in nude mice and also to inhibit neovascularization in a primate model of ischemic retinal disease. In this report, we describe the humanization of muMAb VEGF A.4.6.1. by site-directed mutagenesis of a human framework. Not only the residues involved in the six complementarity-determining regions but also several framework residues were changed from human to murine. Humanized anti-VEGF F(ab) and IgG1 variants bind VEGF with affinity very similar to that of the original murine antibody. Furthermore, recombinant humanized MAb VEGF inhibits VEGF-induced proliferation of endothelial cells in vitro and tumor growth in vivo with potency and efficacy very similar to those of muMAb VEGF A.4.6.1. Therefore, recombinant humanized MAb VEGF is suitable to test the hypothesis that inhibition of VEGF-induced angiogenesis is a valid strategy for the treatment of solid tumors and other disorders in humans.

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